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## Minimal residual disease negativity does not overcome poor prognosis in high risk multiple myeloma: a single center retrospective study

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CK designed the research, interpreted the data, and wrote the paper. HL, KP, ST, AB, SS, DW contributed patients and interpreted the data. LF analyzed the data. PL and RZO designed the research and interpreted the data. EM designed the research, interpreted the data, and wrote the paper.

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### Declaration of Interests

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## Abstract

**Background**—Minimal residual disease (MRD) is a standard measurement for response assessment in multiple myeloma (MM). Despite new treatments, high-risk MM patients continue to have poor prognosis. We evaluated the impact of MRD- in high vs standard- risk patients.

**Methods**—We retrospectively evaluated all consecutive MM patients who had routine MRD testing by 1-tube 8-color advanced flow cytometry with 2,000,000 events and sensitivity level  $10^{-5}$  at our center from 2015–2018 after initial therapy. Kaplan-Meier and log-rank test were used to assess survival estimates and differences between study groups.

**Results**—136 patients with MRD testing after initial therapy/autologous transplant (ASCT) were identified. At a median follow-up of 14 months (1–36 months), Progression-free survival (PFS) and overall survival (OS) were significantly worse in high-risk vs standard-risk patients. During the study period, 50% of high-risk group had progressed (relapse and/or death) vs 20% in standard-risk group ( $p=0.0006$ ). No patients with standard-risk died, but 4 (14%) in the high-risk group did ( $p=0.0007$ ). Regardless of MRD status, high-risk patients had statistically significant worse PFS than standard-risk; at median follow-up 10% standard-risk/MRD-; 20% standard-risk/MRD+; 40% high-risk/MRD-; 45% high-risk/MRD+ had either relapsed or died ( $p=0.0041$ ). MRD status did not impact significantly OS in either group ( $p=0.0914$ ), however longer follow up is needed to assess survival.

**Conclusion**—Genetic abnormalities (FISH/GEP) remain a powerful prognostic indicator for myeloma regardless of MRD status. For newly diagnosed myeloma patients treated with novel triple initial therapy and frontline ASCT, achieving MRD negative status didn't mitigate poor prognosis outcomes of high-risk MM patients.

## Abstract

Overall, patients with multiple myeloma who achieve deep remissions including minimal residual disease negativity have better clinical outcomes when compared to those do not. In this study, we aimed to describe the impact of testing for MRD negativity in a cohort of myeloma patients outside of clinical trial. We found that for most patients MRD negativity does support improved clinical outcomes. However, in our cohort of patients with high-risk myeloma, MRD negativity does not seem to impact the overall poor prognosis.

## Abstract

MRD negativity is associated with improved PFS and OS in multiple myeloma in patients treated on clinical trials. There is less information on MRD testing in patients outside of clinical trials and whether this may be useful clinically. In this study, we describe the clinical outcomes of 136 myeloma patients who had MRD tested outside of clinical trials as per current IMWG response criteria guidelines. In our cohort, patients with low-risk myeloma had improved outcomes if they reached MRD/flow negativity whereas patients with high-risk myeloma had overall poor outcomes regardless of MRD/flow status. MRD status can predict prognosis in patients with multiple myeloma and should be routinely tested, when available, in the clinic, as part of a routine response assessment.

## Keywords

multiple myeloma; newly diagnosed myeloma; minimal residual disease; high-risk multiple myeloma

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## INTRODUCTION

Although multiple myeloma (MM) remains, mostly, an incurable plasma cell disorder, overall survival (OS) and progression free survival (PFS) have improved considerably due to emerging new treatments (1–4). Decades ago, only a fraction of myeloma patients responded to initial therapy. Now, nearly all patients with newly diagnosed myeloma are able to achieve a first remission to treatment (1, 2, 4). In parallel to this progress, response monitoring has also been updated over time from complete remission (CR), to stringent CR (sCR) and now with CR with minimal residual disease negativity (5, 6).

Over the past decade, two meta-analysis showed that both transplant eligible or ineligible MM patients who achieved a CR had longer PFS and OS when compared to patients who did not achieve a CR (7, 8). Despite this, the majority of these patients who had achieved a CR, still relapsed later on. Similarly to other hematologic malignancies such as chronic myeloid leukemia, acute promyelocytic leukemia and acute lymphoblastic leukemia, patients with MM who are in CR and MRD negative had prolonged PFS and OS when compared to those who were in CR MRD positive (9, 10). Several studies have shown that MM patients who achieve a CR MRD negative have significantly better PFS and OS compared to those who don't achieve MRD negativity. These patients in CR MRD positive had, in fact, clinical outcomes that were similar to those patients who only achieved a partial response (PR) or very good partial response (VGPR) (11–25).

Deep MRD monitoring in the bone marrow compartment can be successfully achieved through advanced flow cytometry and next-generation sequencing (NGS). Additionally, extramedullary disease and bone marrow focal lesions can be detected effectively with whole body positron emission tomography/ computed tomography (WB PET/CT) or magnetic resonance imaging (MRI). Although conventional multicolor flow cytometry (MFC) could evaluate and discriminate long-term survival between MRD positive and negative MM patients with high applicability as 90 – 95%, its sensitivity of  $10^{-4}$  to  $10^{-5}$  remained lower than that of molecular methods (Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and NGS) (11, 20–22). Advanced flow cytometry with the appropriate antibody and fluorochrome selections can improve the sensitivity to make it comparable to that of NGS methods (26–29). Importantly, advanced flow cytometry can easily identify hemodilution, is cheaper and has rapid turn-around time. Unfortunately, it does require a fresh specimen, within 24-hour which is actually impractical, and expert dependent (28). Both the International Myeloma Working Group (IMWG) 2016 and the International Clinical Cytometry Society (ICCS) 2016 consensus guidelines recommended that, at a minimum advanced flow cytometry should evaluate at least  $2 - 5 \times 10^6$  total events per sample to detect aberrant plasma cells at a sensitivity of  $10^{-5}$  (6, 30).

The European Myeloma Network has developed a standardized, non-expert-dependent advanced flow cytometry technique called EuroFlow (31, 32). Comparison of Euroflow and conventional 8-color MFC or advanced flow cytometry showed that advanced flow cytometry has higher sensitivity than conventional MFC and was comparable to NGS (26). Memorial Sloan Kettering Cancer Center (NYC, NY) has also developed a 10-color one tube advanced flow cytometry test that has been validated with EuroFlow showing comparable sensitivity (28, 33). MD Anderson Cancer Center (Houston, TX) has been using MFC to measure MRD in myeloma since 2014 (at a sensitivity of  $10^{-4}$ ) and advanced flow cytometry following guidelines from the IMWG and ICCS since 2015 (at a sensitivity of  $10^{-5}$ ) for the routine care of patients with MM. More recently, randomized clinical trials suggest that the depth of MRD negativity also correlates with improved clinical outcomes. Perrot et al evaluated MRD sensitivity in transplant eligible newly diagnosed MM patients treated with bortezomib, lenalidomide and dexamethasone. In this study, they demonstrated that an MRD level of  $10^{-6}$  was predictive of superior PFS when compared to  $10^{-5}$  or  $10^{-4}$  (34). In this study, we set out to describe the clinical outcomes and practice patterns of all consecutive newly diagnosed myeloma (NDMM) patients who had MRD evaluation according to current MRD consensus guidelines at MD Anderson Cancer Center. Additionally, we wanted to describe the implications of reaching MRD negativity in high risk versus standard risk myeloma.

## METHODS

### Patients and treatment

We retrospectively reviewed electronic medical records of all consecutive patients who received standard of care MRD testing from January 2015 to April 2018. The aim of the study was to describe the treatment and practice patterns both in high risk and standard risk NDMM who had MRD testing done as part of standard of care prognosis and disease monitoring. All patients were tested by advanced flow cytometry including at least  $2 \times 10^6$  total events (sensitivity  $10^{-5}$ ) and had MRD testing done at least once either after initial therapy (if patient elected not to proceed with upfront autologous stem cell transplant (ASCT)) or within 6 months after ASCT to evaluate the impact of MRD status in high-versus standard- risk patients. High risk myeloma patients were defined as having positive FISH or cytogenetics for amplification 1q 4 copies and/or t(4;14) and/or t(14;16) and/or deletion 17p and/or high risk gene expression profiling (GEP70, Quest Diagnostics, Secaucus, NJ).

For all patients, initial therapy after diagnosis was either received at MD Anderson Cancer Center or in community centers. Treatment regimens varied according to preference at each center. This study was approved by the MD Anderson Cancer Center Institutional Research Ethics committee.

### Myeloma response assessment

Our center routinely evaluates serum protein electrophoresis, immunofixation, serum free light chains and ratio, and serum immunoglobulin levels at diagnosis at every cycle during initial therapy, at 3 months after ASCT, and monthly during the maintenance phase.

Response and MRD were assessed by IMWG 2016 consensus criteria (6). NDMM patients who achieved at least a PR after initial therapy for myeloma (if no transplant was done) or within 6 months after ASCT (if upfront transplant was done) and before maintenance therapy was initiated were eligible. In our center, some patients with less than a CR are tested for MRD. These are patients whose bone marrow biopsies are requested after a pre-set amount of treatment cycles, who are responding to therapy and who are believed to be close to VPGR or CR status. Given discomfort and cost of bone marrow biopsy procedures, our center errs on the side of caution and orders MRD testing in responding patients as repeat bone marrow biopsy for the sole purpose of checking MRD status may not be feasible. Patients with PR or VGPR who had a negative MRD test are labeled as “flow negative at MRD level of detection” and are not thought of as being in CR.

### MRD assessment

MRD by advanced flow cytometry was initiated at MD Anderson in 2015 according to consensus guideline practices (35, 36). Bone marrow specimens were prepared with a pre-lysis technique within 24 hours after bone marrow aspiration collection. Routinely, we use an 8-color 1 tube panel, consisting of CD138, CD38, and CD45 to identify the total number of plasma cells, combined with CD19, CD27, CD81, CD59, and CD117 to identify abnormal plasma cells. Abnormal plasma cells are identified when they express two or more aberrant markers. A second tube which comprises of CD138, CD38, CD45, CD56, polyclonal cytoplasmic kappa light chain and polyclonal cytoplasmic lambda light chain is applied when the first tube cannot obtain adequate data. The total number of events included was at least 2,000,000 events to detect 20 aberrant cells with a lower limit of detection is  $1 \times 10^{-5}$ .

### Statistical analysis

Descriptive statistics including mean, standard deviation, median, and range for continuous variables such as number of aberrant cells, and frequency counts and percentages for categorical variables such as MRD status and level of risk were done. Kaplan-Meier method was used to estimate the time-to-event endpoints including PFS and OS. PFS was calculated from the date of MRD testing until disease progression or death. OS was calculated from the date of MRD testing to the date of death. The log-rank test was used to evaluate the difference in the time-to-event endpoints between/among patient groups. Statistical software SAS 9.4 (SAS, Cary, NC) and S-Plus 8.2 (TIBCO Software Inc., Palo Alto, CA) were used for the analyses. Multivariate analysis was not performed due to the limited number of events. Cox proportional hazards model was fitted for covariate R-ISS.

## RESULTS

### Patients

A total 960 MRD flow cases were done at MD Anderson for MM patients from January 2015 until April 2018. Of these, only 370 cases tested a minimum of 2 million total events. From these 370 MRD cases, 152 cases were excluded because they did not meet eligibility criteria (Figure 1). From the remaining 218 cases, 170 cases were tested in NDMM, 2 cases were tested in patients when they were NDMM and then again later on as they relapsed from

initial treatment (RRMM) and 46 cases were tested in RRMM only. From these 172 cases, only 136 were tested in patients who were NDMM and had at least a PR after initial therapy (if patient elected not to proceed with upfront ASCT) or within 6 months after ASCT.

Patients' baseline characteristics and treatments are described in Table 1. Median age for all patients was 61 years old (range, 28–83) and 33% of patients were older than 65 year-old. 127 patients (93%) received initial therapy with at least 3 agents and 133 patients (98%) were treated with novel agents. The most frequently used initial therapy regimens were carfilzomib, lenalidomide or cyclophosphamide and dexamethasone (n=63, 46.3%) and bortezomib, lenalidomide/thalidomide or cyclophosphamide and dexamethasone (n=60, 44%). 29 patients (22%) had high-risk myeloma. Ninety percent of patients had an upfront ASCT. All patients for whom maintenance information was available (n=107, 78%) received continued therapy after initial treatment or ASCT and the majority of them received lenalidomide maintenance (n=62, 58%). Twenty out of 29 high-risk patients had maintenance information. Seventy-five percent of patients (15/20 patients) received three-drug combination (five with carfilzomib/ lenalidomide/dexamethasone, five with elotuzumab/lenalidomide/dexamethasone, three with ixazomib/ lenalidomide/dexamethasone, one with carfilzomib/pomalidomide/dexamethasone, and one with bortezomib/ lenalidomide/dexamethasone) as maintenance therapy and the other five patients received either lenalidomide alone (n=4) or pomalidomide/dexamethasone (n=1). The majority of patients in our center underwent upfront ASCT (n=123, 90%) with the oldest patient having an upfront ASCT at 83 years of age. The median age of upfront ASCT versus non-(or delayed) ASCT was 61 (range, 28 – 83) vs 58 (range, 32 – 75), respectively (p= 0.185).

### Minimal residual disease status

A total of 72 patients (53%) achieved MRD negativity or were flow negative at MRD level after initial therapy with or without upfront ASCT. In particular, 31 out of 69 (44.93%) NDMM patients achieved MRD negativity post initial treatment without upfront ASCT; whereas, 52 out of 82 (63.4%) NDMM patients achieved MRD negativity within 6 months post upfront ASCT. 13 patients had MRD testing done after initial therapy/before upfront ASCT and after ASCT. Among these 13 patients, 4 patients had persistent MRD positivity, 6 patients had MRD turn negative from positive and 3 patients had persistent MRD negativity after upfront ASCT when compared to measurements before ASCT. In our study, only 8% of patients who were in CR (sCR+CR) were MRD positive, whereas 83% of patients who had a PR were flow positive at MRD level of detection (p<0.001) (Table 2). In the high-risk patient group, 50% of patients in CR where MRD negative (n=7/15) whereas only 38% of those not in CR (PR/VGPR) were flow negative at MRD level (n=4/12) (Table S1).

### Minimal residual disease status and genetic risk

Genetic data was available for 129 patients, 100 (78%) of whom were standard risk and 29 (22%) were high risk MM. 54 (54%, n=54/100) patients with standard risk myeloma and 12 (41%, n=12/29 patients) with high risk myeloma were MRD negative after initial therapy with or without ASCT (p=0.233). In detail, 8 out of 14 patients (57.1%), 4 out of 11 patients (36.4%), 1 out of 2 patients (50%), and 2 out of 4 patients (50%) with monosomy 17,

t(4;14), amplification 1q 4 copies, and high GEP70 score reached MRD negativity, respectively. The rate at which standard or high-risk myeloma achieved MRD negativity or were bone marrow flow negative at MRD level of detection was not statistically different ( $p=0.23$ ) in these series of 29 high risk myeloma patients (Table 1).

### Survival outcomes

For all patients ( $n=136$ ), at a median follow-up of 14 months (1–36 months), median PFS and OS were not reached (Figure 2 and 3). One- and two-year PFS were 85.3% (95% CI= 79.4% – 92.7%) and 73.3% (95% CI=59.7% – 90%) (Figure 2). Of the 136 patients, 19 patients relapsed. Of these 19 patients, 10 out of 29 (35.5%) were high risk patients and 9 out of 100 (9%) patients were low risk,  $p=0.001$ .

According to MRD status, 7 out of 72 MRD negative patients and 12 out of 64 MRD/flow positive patients experienced disease relapse. Patients who were MRD/flow negative and MRD/flow positive had 1- and 2- year PFS at 90% (95% CI= 82% – 98%) versus 81% (95% CI= 71% - 93%) and 83% (95% CI= 69% – 99%) versus 65% (95% CI= 45% - 93%), respectively ( $p=0.1647$ ). Low risk patients had significantly better PFS than high risk patients. 92% (95% CI= 86% – 98%) versus 64% (95% CI= 47% – 87%) and 79% (95% CI= 62% – 100%) versus 51% (95% CI= 30% – 87%) of standard- and high-risk patients survived without disease progression or death at 1 and 2 year, respectively ( $p=0.0006$ ). Interestingly, at a sensitivity of  $10^{-5}$ , high risk patients showed significantly worse PFS and OS, regardless of MRD status (Figure 2 and 3). At the median follow up of 14 months, 10% standard-risk/MRD negative; 20% standard-risk/MRD positive; 40% high-risk/MRD negative 45% high-risk/MRD positive had either relapsed or died ( $p=0.0041$ ). Median OS for high-risk patients (either those who were CR/MRD negative or non-CR/flow negative) was not reached ( $p=0.175$ ). Median PFS for high-risk patients in CR and MRD negative was not reached, however the median PFS for high-risk patients who were not in CR and flow negative was 23 months ( $p=0.495$ ). (Figure S1 and S2). No statistical significant differences were observed in PFS or OS in patients with high-risk myeloma by MRD/flow or CR status (Figures S3–S8).

In our cohort, 4 patients died during this follow-up time and all of them had high-risk MM. Three of them had t(4;14) and R-ISS stage III and one of them had deletion 17p (Figure 3). The hazard ratio for progression or death in 107 patients with available data for R-ISS stage was: 12.65 for R-ISS 2 versus 1 (95% CI: 1.57 ~ 101.85) and 32.25 (95% CI: 3.54 ~ 293.49) for R-ISS 3 versus 1 ( $p=0.007$ ).

## DISCUSSION

In this single center, retrospective study we aimed to evaluate the relationship between MRD status after initial therapy in NDMM with clinical outcomes in consecutively treated patients outside of a clinical trial. We had previously reported our experience using MFC at a sensitivity of  $10^{-4}$  in a total of 95 patients to report MRD outcomes (37). Here, we report on a larger series of patients using advanced flow cytometry with a higher sensitivity as established by IMWG and ICCS MRD guidelines.

The MRD rate in this cohort of patients was 53% after either initial therapy or ASCT. Most of our patients received initial therapy with either VRD (n=43, 32%) or KRd (n=60, 44%). The Intergroupe Francophone du Myelome (IFM) 2009 study comparing VRD with delayed versus upfront ASCT in NDMM patients reported MRD negative rates of 65% versus 79%, respectively (38). Lower MRD negative rates in our patient cohort can be explained by a shorter duration of initial therapy (especially in the cohort of patients that had MRD tested after initial therapy which is usually given for 2–4 months in our center and without undergoing transplantation). In addition, almost a half of this cohort used KRd as first-line treatment. Some of us, had reported a higher MRD negative rate of 92% in 45 KRd-treated NDMM patients after 8 months of therapy (24). However, cross comparisons are difficult since most of our patients receive 2–4 months of initial KRd therapy instead of 8 months. In the future, to increase the rates of MRD negativity in our patient population and, perhaps to improve clinical outcomes, one could consider prolonging the time of initial therapy before transplant to 4–6 months or adding a fourth agent (i.e. CD38 monoclonal antibody). This is in line with other reports suggesting that patients with NDMM treated with KRd take, on average, 6 months to reach MRD negativity (39). Gu et al using advanced flow cytometry at  $10^{-5}$  sensitivity in 104 NDMM patients showed an MRD negativity rate of 36.5% which is a little lower than the one reported in this study (17).

The median PFS was not reached both for MRD negative and positive patients. The 1- and 3-year PFS tended to be better in MRD negative patients, 90% versus 81% and 83% versus 65% (p=0.1647). This difference in PFS between MRD negative and positive patients may be non-significant because of the short follow-up time, the low incidence of relapsed disease or the depth of MRD detection level used in this study of  $10^{-5}$  instead of the deeper  $10^{-6}$  level sensitivity level. Other studies have shown that MRD status does impact PFS (9, 10, 17, 24, 40). In contrast, the impact of MRD status on survival in high-risk NDMM patients remains more controversial. Our study continues to show that patients with high risk myeloma have a much higher rate of early relapse or death than low risk myeloma, even when treated with initial novel triple therapy, including KRd, as 35% (10/29 patients) of high risk versus 9% (9/100 patients) (p=0.001) of low risk patients relapsed or died during follow up. This was true even for patients who had high risk myeloma and were MRD negative. The 1-year PFS rate was 90%, 80%, 60%, and 55% in standard-risk/MRD negative, standard-risk/MRD positive, high-risk/MRD negative, and high-risk/MRD positive, respectively (p=0.0041). Detailed analysis performed on our cohort of high-risk patients by either CR or MRD/flow status did not show any statistically significant differences in PFS or OS between CR/non-CR patients or MRD/flow negative or positive patients. This may be due to the small number of patients in the high-risk cohort (n=29), short follow up and low number of progression/death events. Larger cohorts, longer follow up and higher levels of sensitivity of MRD test (i.e.  $10^{-6}$ ) may be needed to show a difference in PFS/OS in high-risk myeloma patients who are in CR/non-CR and reach MRD/flow negativity status.

Deletion (17p), t(4; 14) and t(14; 16) are genetic abnormalities that are well known to correlate with worse outcomes in myeloma and are widely regarded as high risk according to the IMWG classification. Our study also included amplification of 1q in 4 or more copies and high risk score GEP70 because they are linked to poor outcomes (41–44). Our rates of



MRD negativity in high versus low risk myeloma- 41.4% vs 54%, respectively ( $p=0.233$ )- are similar to those reported by others (23, 25, 45). Similar to our findings, others have reported that despite reaching MRD negativity, high-risk myeloma continues to be an independent factor for poor prognosis (14, 46). In contrast, four other studies using advanced flow cytometry at  $10^{-5}$  (47) or NGS with a sensitivity of  $10^{-6}$  (23, 25, 45) have shown that high risk myeloma patients who achieve MRD negativity have similar PFS and OS to those in the low risk group. More studies are needed in particular in high risk myeloma to evaluate the impact of MRD on risk status including the sensitivity threshold for MRD testing in this particular group. It has been reported that only around 10% of patients with deletion 17p could become MRD negative (23, 25, 45) which was different from the results on our study where deletion 17p patients could achieve MRD negativity in 57% of patients. This difference might be because half of our patients received more intense initial regimens such as KRd.

Some of our limitations are the nature of this study being retrospective with the possibility of the introduction of bias and short median follow up of only 14 months counted from the date that MRD testing was performed. Moreover, outcomes were evaluated based on a one-time MRD assessment. Our study is valuable in reporting clinical outcomes in patients with myeloma using advanced flow cytometry MRD for prognosis and monitoring as part of a standard of care response assessment tool. It provides further evidence that, in low risk myeloma, MRD is a good predictor of outcomes, however, in high risk myeloma more studies are needed to evaluate the role of MRD status in prognosis. In the future, serial monitoring of MRD status during initial therapy, ASCT and maintenance may be more informative to predict prognosis to make treatment decisions (17).

MRD status after initial therapy determines clinical outcomes in myeloma. However, high-risk genetics and GEP remain factors that predict prognosis independently of MRD status. Deeper sensitivity, serial MRD monitoring, evaluation of myeloma biology and the use of MRD guided treatment may be helpful in the future to improve survival for all patients with multiple myeloma.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

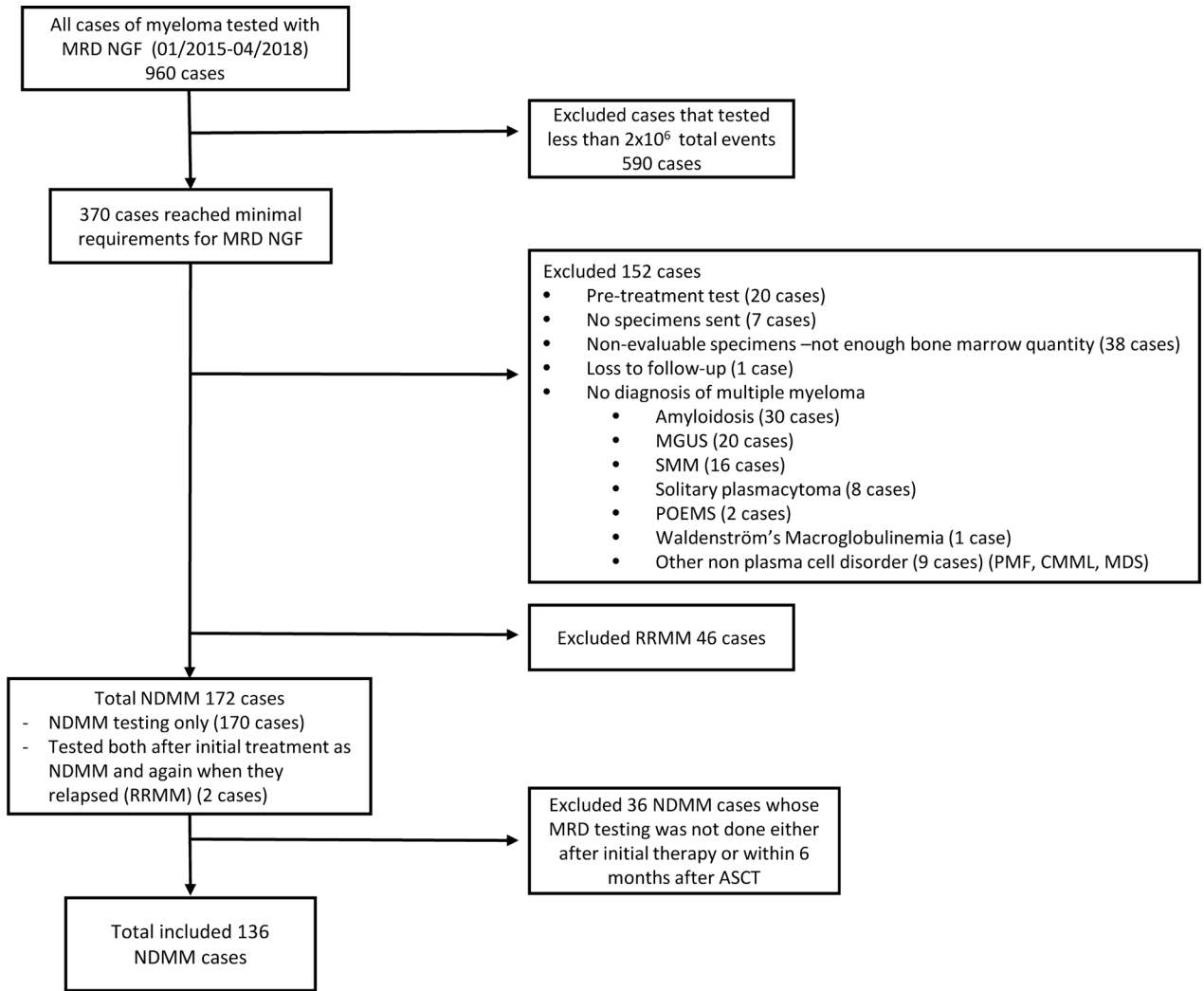
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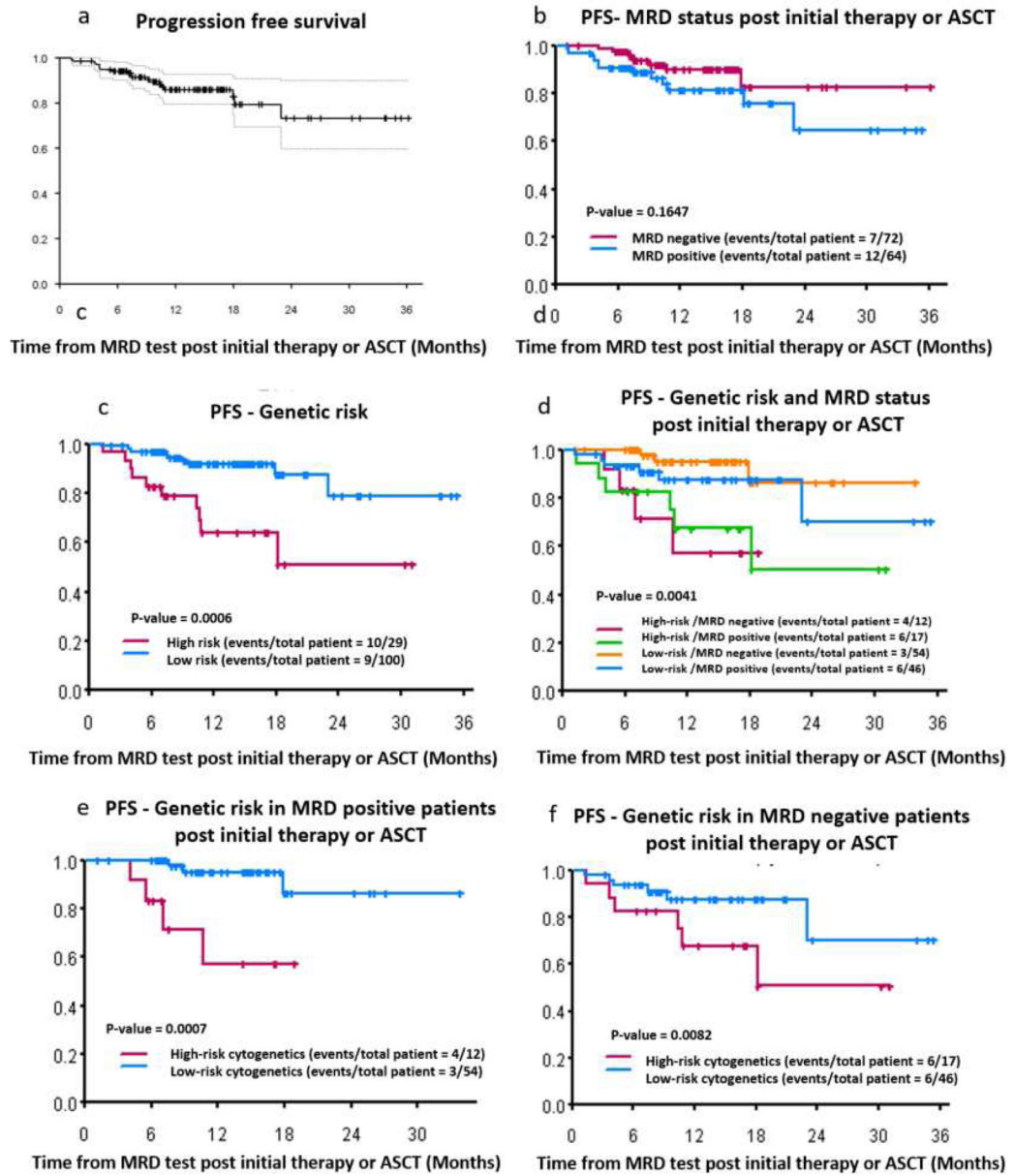
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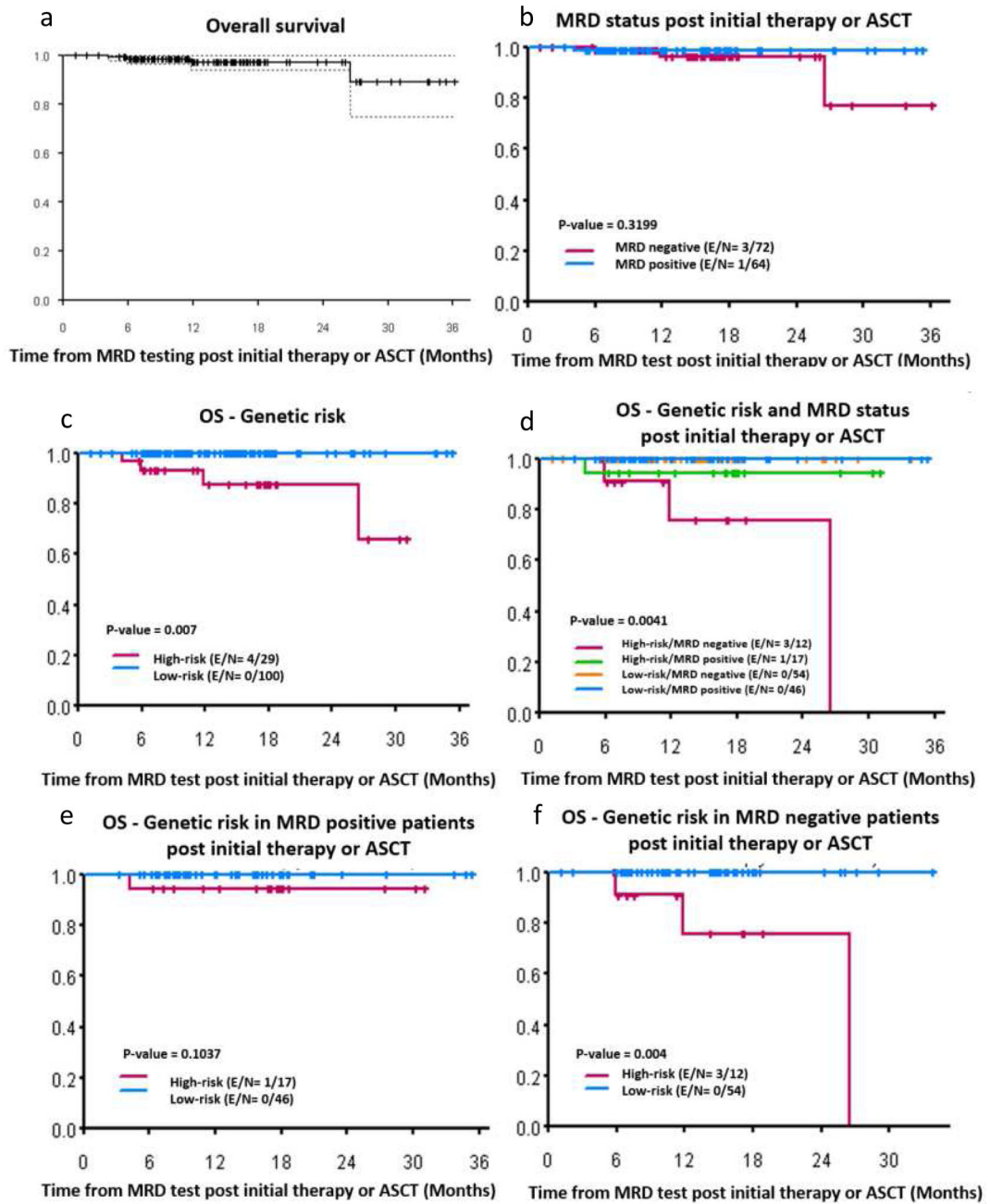
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**Figure 1:**  
Trial flow.



**Figure 2:** Clinical outcomes (all patients n=136). (a) Progression free survival for all patients (n=136), (b) PFS by MRD status post initial therapy or ASCT, (c) PFS by high versus low/standard risk myeloma patients, (d) PFS according to genetic risk and MRD status, (e) PFS according to genetic risk in MRD positive patients, (f) PFS according to genetic risk in MRD negative patients



**Figure 3:**

Clinical outcomes. (a) Overall survival for all patients (n=136), (b) OS by MRD status post initial therapy or ASCT, (c) OS by high versus low/standard risk myeloma patients, (d) OS according to genetic risk and MRD status, (e) OS according to genetic risk in MRD positive patients, (f) OS according to genetic risk in MRD negative patients

**Table 1:**

Baseline characteristics, transplant status and treatments received.

	All patients n=136/100%	MRD negative or flow negative at MRD level post initial therapy or ASCT; n=72 /53%	MRD positive post initial therapy or ASCT; n=64 /47%	p-value (comparing MRDpos and MRDneg)
Age, median (range)	61 (28, 83)	62 (32, 83)	59 (28, 79)	0.233
Sex, n (%)				0.5771
-Male	82 (60.29)	45 (62.5)	37 (57.8)	
-Female	54 (39.71)	27 (37.5)	27 (42.2)	
Diagnosis, n (%)				0.6908
-MM	110 (80.9)	57 (79.1)	53 (82.8)	
-Prior MGUS/SMM that progressed to MM	12 (8.8)	7 (9.7)	5 (7.8)	
-MM with amyloidosis	6 (4.4)	2 (2.8)	4 (6.2)	
-Prior solitary plasmacytoma that progressed to MM	2 (1.5)	2 (2.8)	0	
-Extramedullary myeloma	4 (2.9)	3 (4.2)	1 (1.6)	
-Plasma cell leukemia	2 (1.5)	1 (1.4)	1 (1.6)	
Type, n (%)				0.2090
-IgG kappa	42 (30.9)	24 (33.3)	18 (28.1)	
-IgG lambda	27 (19.9)	8 (11.1)	19 (29.7)	
-IgA kappa	21 (15.4)	14 (19.4)	7 (10.9)	
-IgA lambda	7 (5.1)	4 (5.6)	3 (4.7)	
-IgM lambda	1 (0.7)	0	1 (1.6)	
-IgD kappa	1 (0.7)	0	1 (1.6)	
-IgD lambda	3 (2.2)	2 (2.8)	1 (1.6)	
-Kappa light chain only	19 (14)	12 (16.7)	7 (10.9)	
-Lambda light chain only	9 (6.6)	4 (5.6)	5 (7.8)	
-Non-secretory	5 (3.7)	3 (4.2)	2 (3.1)	
-IgG kappa and IgA kappa	1 (0.7)	1 (1.4)	0	
Genetic risk stratification <sup>*,**</sup>				0.2313
-Low risk	100 (77.52)	54 (81.8)	46 (73)	
-High risk	29 (22.48)	12 (18.2)	17 (27)	
Deletion 17p (n=129)	14 (10.9)	8 (11)	6 (10.7)	0.512
t(4; 14) (n=129)	11 (8.5)	4 (6.1)	7 (11.1)	0.306
Amp 1q 4 copies (n=117)	2 (1.7)	1 (1.6)	1 (1.8)	0.952
High risk GEP70 (n=5)	4 (80)	2 (100)	2 (66.7)	0.414
ISS (n=114), n (%)				0.723
-1	64 (56.1)	34 (58.6)	30 (53)	
-2	23 (20.2)	10 (17.2)	13 (23.2)	



	All patients n=136/100%	MRD negative or flow negative at MRD level post initial therapy or ASCT; n=72 /53%	MRD positive post initial therapy or ASCT; n=64 /47%	p-value (comparing MRDpos and MRDneg)
-3	27 (23.7)	14 (24.1)	14 (23.2)	
R-ISS (n=109), n (%)				
- 1	47 (43.1)	25 (43.1)	22 (43.1)	0.9612
- 2	46 (42.2)	24 (41.4)	22 (43.1)	
- 3	16 (14.7)	9 (15.5)	7 (13.7)	
Initial therapy received, n (%)				0.1618
-KRD	60 (44.1)	29 (40.3)	31 (48.4)	
-KCD	3 (2.21)	3 (5.2)	0	
-VRD	43 (31.62)	26 (37.1)	17 (26.6)	
-VTD	1 (0.74)	1 (1.4)	0	
-VCD	16 (11.8)	8 (11.1)	8 (12.5)	
-VD	5 (3.7)	4 (5.6)	1 (1.6)	
-RD	4 (2.9)	0	4 (6.3)	
-Panobinostat-VRD	1 (0.7)	0	1 (1.6)	
-MPT	1 (0.7)	0	1 (1.6)	
-mCBAD	2 (1.5)	1 (1.4)	1 (1.6)	
ASCT	123 (90.4)	65 (90.3)	58 (90.6)	0.9452
Maintenance regimens (n=107) ***				0.8685
-Elotuzumab/Len+/-D	29 (27.1)	15 (27.3)	14 (26.9)	
-Ixazomib/Len+/-D	7 (6.5)	4 (7.3)	3 (5.8)	
-Ixazomib alone	1 (0.9)	1 (1.8)	0	
-KRD or KPD	4(3.7)	1(1.8)	3 (5.8)	
-FRD	1 (0.9)	0	1 (1.9)	
-Len+/-D	62 (57.9)	33 (60)	29 (55.8)	
-Bortezomib alone	2 (1.9)	1 (1.8)	1 (1.9)	
-Thalidomide/D	1 (0.9)	0	1 (1.9)	

Abbreviations: Amp, amplification; D, dexamethasone; FRD, panobinostat/lenalidomide/dexamethasone; GEP70, gene expression profiling done at baseline (Quest Diagnostics, Secaucus, NJ; Ig, immunoglobulin; KCD, carfilzomib/cyclophosphamide/dexamethasone; KRD, carfilzomib/lenalidomide/dexamethasone; KPD, carfilzomib/pomalidomide/dexamethasone; Len, lenalidomide; mCBAD, modified Cyclophosphamide, Bortezomib, Doxorubicin, and Dexamethasone; MGUS, monoclonal gammopathy undetermined significance; MM, multiple myeloma; MPT, melphalan/prednisolone/thalidomide; n, number; RD, lenalidomide/dexamethasone; R-ISS, Revised Multiple Myeloma International Staging System; SMM, Smoldering multiple myeloma; VCD, bortezomib/cyclophosphamide/dexamethasone; VD, bortezomib/dexamethasone ; VRD, bortezomib/lenalidomide/dexamethasone; VTD, bortezomib/thalidomide/dexamethasone.

\* High risk genetics were defined as presence of at least one of the following abnormalities: t(4,14), t(14,16), deletion 17p, amplification 1q > 4 copies or high risk GEP70.

\*\* Risk stratification data were available for 129 patients for deletion 17p and t(4;14), 117 patients for amplification of 1q and 5 patients for GEP70.

\*\*\* Maintenance information was available for 107 patients.

**Table 2.**

MRD status by IMWG response assessment.

	MRD negative (n=72)	MRD positive (n=61)	p-value
sCR + CR (n=59), n(%)	54 (91.5)	5 (8.5)	< 0.001
VGPR* (n=44), n(%)	13 (29.5)	31 (70.5)	
PR* (n=30), n(%)	5 (17)	25 (83)	

\* Patients with either VGPR or PR are considered to be flow bone marrow aspirate negative at MRD level of detection rather than MRD negative.

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